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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/741,669	FORSYTH ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-56,128,132,134 and 135* is/are pending in the application.

4a) Of the above claim(s) *128 and 132* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-56,134 and 135* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3/2004* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *5/2004* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on November 15, 2004 has been entered. The claims pending in this application are claims 45-56, 128, 132, 134, and 135 wherein claims 128 and 132 have been withdrawn from consideration as the result of the restriction requirement. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on November 15, 2004.

Election/Restrictions

2. This application contains claims 128 and 132 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

3. The examiner has signed Form PTO-1449 filed on March 19, 2004 and attached the Form PTO-1449 with this office action. However, the examiner noted that the reference WO01/02605 was not available when the examiner wrote previous office action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 45-56, 134, and 135 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing certain sensitized microbial cell as recited in claims 45-56, 133, and 134 by expressing a sub-lethal level of an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60, does not reasonably provide enablement for producing any kind of sensitized microbial cell as recited in claims 45-56, 134, and 135 by expressing a sub-lethal level of any kind of antisense nucleic acid complementary to a nucleic acid in any kind of microbial cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance to produce any kind of sensitized microbial cell as recited in claims 45-56, 134, and 135 by expressing a sub-lethal level of any kind of antisense nucleic acid complementary to a nucleic acid in any kind of microbial cell. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no

predictability whether any kind of sensitized microbial cell recited in claims 45-56, 134, and 135 can be produced.

Claims 45-56, 133, and 134 are directly to a method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism by expressing a sub-lethal level of any kind of antisense nucleic acid complementary to a nucleic acid in any kind of microbial cell in order to inhibit the expression of a yidC gene product in any kind of microbial cell including *E. coli* cell. The specification only describes SEQ ID No: 60, which is a nucleotide sequence of Yid C from *E.Coli* wherein Yid C is a protein that can mediate membrane protein assembly in bacteria (see a review from Chen *et al.*, Biol. Chem., 383, 1565-1572, October 2002). Applicant's declaration under 37 C.F.R § 1.132 filed on August 11, 2003 (see page 3, fifth paragraph) showed that a sensitized *E. Coli* can be produced by expressing a sub-lethal level of an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60. However, the specification does not provide a guidance to produce any kind of sensitized microbial cell as recited in claims 45-56, 134, and 135 by expressing a sub-lethal level of any kind of antisense nucleic acid complementary to a nucleic acid in any kind of microbial cell wherein said antisense nucleic acid is either complementary to mRNA of yidC or complementary to mRNA that is not encoded by yidC gene. First, although SEQ ID No: 60 can be used as an antisense nucleic acid in *E.coli,* since a microbial cell can be defined as an organism of microscopic size including bacteria, fungi, algae, and protozoa, it is unclear whether any kind of antisense nucleic acid complementary to a nucleic acid in any kind of microbial cell, wherein said antisense nucleic acid is either complementary to mRNA of yidC or complementary to mRNA that is not encoded by yidC gene, can be used as an antisense nucleic acid in any kind of

microbial cell as recited in claims 45-56, 134, and 135. Second, it is known that the art of antisense therapy is highly unpredictable (see Bennett, Biochem Pharmacol. 55:9-19, 1998, page 9, col.1, line 19-23). The art clearly emphasize that expectations of current antisense therapy has been over sold and has factually provided only a limited success (see Branch, TIBS, 23 Feb.,45-50, 1998, page 46 col.2. para.3; Gura, Science 270:575-577, 1995). Because it is difficult to predict the what portion of an RNA molecule would be accessible in-vivo, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside the cells. The efficacy of antisense therapy is further compounded by the fact that base compositions as well as the secondary and tertiary structure of the target nucleotide sequence determines the accessibility of the sequence to an antisense sequence (see Branch, page 47 col.2 para.3, page 49, col.1, para 3). Furthermore, in inside cells, it is not possible to improve antisense specificity by rising temperature or ionic strength, therefore alternative strategies are required to enhance specificity within cells (see Branch, page 48, col.3, para.3). Since claims 45-56, 134, and 135 do not limit an antisense nucleic acid to SEQ ID NO: 60 and the specification does not provide an evidence to show that yidC cDNA or gene is highly conserved in all microbial cell, in view of the specification and 37 C.F.R § 1.132 filed on August 11, 2003, it is unclear whether any portion of yidC from one microbial cell can be used as an antisense nucleic acid to inhibit the expression of a yidC gene product in any kind of microbial cell. In fact, sequence searching shows that highly conserved region of SEQ ID No: 60 (a nucleotide sequence of yid C from *E.Coli*) only can be found in bacteria strain *Shigella flexneri* 2a, *E. Coli,* and *Salmonella enterica suvbsp. Enterica serova Typhi* (see attached sequencing

search results in the office action mailed on January 8, 2004). This suggests that a cDNA of yidC or SEQ ID NO: 60 cannot be used as an antisense nucleic acid in any kind of microbial cell.

With these unpredictable factors, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. These undue experimentation at least includes to test whether a sensitized microbial cell as recited in claims 45-56, 134, and 135 can be produced by expressing a sub-lethal level of any kind of antisense nucleic acid complementary to a nucleic acid in any kind of microbial cell.

Response to Arguments

In page 7, last paragraph bridging to page 12, second paragraph of applicant' remarks, applicant argues that method recited in claims 45-56, 134, and 135 is enable because "the specification explicitly describes (1) how to identify a yidC homolog in a microorganism having a yidC gene; and (2) how to obtain an antisense nucleic acid capable of inhibiting the expression of the product of the yidC homolog and how to use that antisense nucleic acid to sensitize the microbial cell from which the yidC homolog was identified" and "[A]s set out in the Declaration, Applicants have (1) identified the yidC homolog in *Staphylococcus aureus*, (2) identified antisense nucleic acids capable of inhibiting the expression of the yidC gene product, and (3) shown that these antisense nucleic acids are capable of inhibiting the proliferation of (sensitizing) *Staphylococcus aureus*. These experiments, which are described in detail in the Declaration, were performed substantially as described in the instant application and were completed without difficulty. In particular, Applicants identified a number of different antisense nucleic acids complementary to the *S. aureus* yidC gene, which when expressed in *S. aureus*,

inhibited its proliferation. Results of experiments in which the level of inhibitory antisense expression was varied, indicated that increasing the level of antisense expression increased the inhibition of proliferation (see Declaration). As a second example, the Declaration also describes a second inhibitory antisense nucleic acid obtained from E. coli (totally separate from and independent of SEQ ID NO: 60) which is complementary to at least a portion of the yidC gene. This second antisense nucleic acid, which was identified using the methods described in Examples 1 and 2 of the instant patent application, shares no overlap with SEQ ID NO: 60 but has the ability to inhibit E. coli proliferation to the same extent as SEQ I'D NO: 60".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, because it is difficult to predict the what portion of an RNA molecule would be accessible in-vivo, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside the cells. The efficacy of antisense therapy is further compounded by the fact that base compositions as well as the secondary and tertiary structure of the target nucleotide sequence determines the accessibility of the sequence to an antisense sequence (see Branch, page 47 col.2 para.3, page 49, col.1, para 3). Furthermore, in inside cells, it is not possible to improve antisense specificity by rising temperature or ionic strength, therefore alternative strategies are required to enhance specificity within cells (see Branch, page 48, col.3, para.3). Since claims 45-56, 134, and 135 do not limit an antisense nucleic acid to SEQ ID NO: 60 and the specification does not provide an evidence to show that yidC cDNA or gene is highly conserved in all microbial cell, in view of the specification and 37 C.F.R § 1.132 filed on August 11, 2003, it is unclear whether any portion of yidC from one microbial cell can be used as an antisense nucleic acid to inhibit the expression of

a yidC gene product in any kind of microbial cell. In fact, sequence searching shows that highly conserved region of SEQ ID No: 60 (a nucleotide sequence of yid C from *E.Coli*) only can be found in bacteria strain *Shigella flexneri* 2a, *E. Coli,* and *Salmonella enterica suvbsp. Enterica serova Typhi* (see attached sequencing search results in the office action mailed on January 8, 2004). This suggests that a cDNA of yidC or SEQ ID NO: 60 cannot be used as an antisense nucleic acid in any kind of microbial cell. Second, although applicant shows several yidC antisense nucleic acid from either *E. Coli* or *S. aureus* in 37 C.F.R § 1.132 filed on August 11, 2003, applicant does not show that these antisense nucleic acid can be used as an antisense nucleic acid to inhibit the expression of a yidC gene product in any kind of microbial cell as recited in claim 45.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 45-56, 134, and 135 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 45 is rejected as vague and indefinite because, from step (a) of the claim, it is unclear whether an antisense nucleic acid is inside of a microbial cell or not. Furthermore, it is unclear that an antisense nucleic acid is complementary to yidC gene or not. Please clarify.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. No claim is allowed.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
February 1, 2005

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
2/2/05